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EXAMINER	
NIEBAUER, RONALD T	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/572,239	VAN NORREN ET AL.	
	Examiner	Art Unit	
	RONALD T. NIEBAUER	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-36* is/are pending in the application.

4a) Of the above claim(s) *20-22,26,27 and 30-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,23-25,28-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments and arguments filed 10/29/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 1-18 have been cancelled. Claims 19,25 have been amended.

As noted previously, Applicant's election with traverse of Group II (claims 19-29) and the following species:

Guanosine equivalent (GTP increasing component) – GUANOSINE

Carbohydrate – GLUCOSE

(no other species were identified for the composition)

in the reply filed on 2/22/08 is acknowledged.

Claims 20-22,26-27,30-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention/species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/22/08. In particular claims 30-36 are drawn to a non-elected group and claims 20-22,26-27 are drawn to non-elected species.

Claims 19,23-25,28-29 are under consideration.

Claim Rejections - 35 USC § 112

Previously, claims were rejected under 112 2nd. Since the claims have been amended the rejection has been updated due to the amendments.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19,23-25,28-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites that the claims are drawn to methods of prevention specifically for mammals suffering from trauma. Claim 25 recites that the administration is prior to the occurrence of the trauma. As such, it is unclear if the patient population is or is not suffering from trauma. The recitation of claim 18 'suffering from trauma' implies that the patient population is suffering from trauma. However, claim 25 states that the administration is prior and it is known that preventative measures can be administered prior to the onset of an ailment. As such, the scope of the claims is unclear.

Claim 19 and dependent claims are drawn to methods of administering compositions where the composition comprises '…ribose nucleobase adduct, ribose ester'. It is unclear if the ribose nucleobase adduct and the ribose ester are alternative elements. If so the amount of the ribose ester is unclear. It is unclear what specific structural features are part of the adduct. It is unclear if the adduct is the product of a ribose nucleobase and a ribose ester or if it is the product of other components.

Claim 29 refers to 'guanosine equivalents'. The specification page 5 lines 19-23 provides a definition for 'guanosine equivalents'. However, the scope of 'guanosine equivalents' remains unclear. In particular the definition recites that 'precursors of guanosine' are encompassed in the definition. The term 'precursors of guanosine' is unclear. In particular it is unclear if any

compound involved in a chemical synthesis or a biological pathway including guanosine would be considered a precursor.

As amended claim 19 states that there is at least 20 g/l of the digestible water soluble carbohydrate and at least 10 g/l of the digestible water soluble carbohydrate. It is unclear if there is more than more water soluble carbohydrate. If there is only one water soluble carbohydrate it is unclear if the 20g/l or the 10g/l language is controlling.

Response to Arguments 112 2nd

Since the claims have been amended, a new rejection adapted to the claims is recited above. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that claim 25 has been amended to depend from claim 23. Applicants argue that it is clear that claim 19 is directed to patients who have or will suffer from trauma. Applicants argue that 'guanosine equivalents' have been deleted from the claims.

Applicant's arguments filed 10/29/08 have been fully considered but they are not persuasive.

Although Applicants argue that claim 25 has been amended to depend from claim 23, the claims remain unclear. If one were to incorporate the language of claim 24 into claim 19 the claim would read on those suffering from prescheduled surgery. However, 'suffering from prescheduled surgery' is not a term of the art and one would not recognize the metes and bounds of such phrase, leading to multiple interpretations of the phrase. Further, although Applicants argue that claim 19 recites the method is for a mammal suffering from trauma (page 15 of reply), it is noted that applicants state (page 11 of reply) that claim 19 is drawn to patients who have or

will suffer from trauma. Those who will suffer from trauma do not necessarily have trauma. As such the applicants contradictory arguments that the patient is one who suffers from trauma yet is one who is not yet suffering from trauma is evidence that the metes and bounds of the claims are unclear.

Although Applicants argue that it is clear that claim 19 is directed to patients who have or will suffer from trauma, such language is not found in the claims.

Although Applicants argue that 'guanosine equivalents' have been deleted from the claims, the terminology remains in claim 29.

Previously, claims were rejected under 112 1st - enablement. Since the claims have been amended the rejection has been updated due to the amendments.

Claims 19,23-25,28-29 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention:

The claims are drawn to methods of preventing multiple organ dysfunction.

Although the claims are unclear (see 112 2nd) the claims are given the broadest reasonable interpretation (see MPEP section 2111). Since the claims are drawn to administration prior to the occurrence of trauma (see claim 25) the claims are interpreted as being open to administration prior to any type of trauma. The guanosine equivalents recited in claim 29 have been interpreted as referring to guanosine, otherwise the claim would not further limit the previous claim. The claims have been interpreted such that there is at least one soluble carbohydrate of at least 10 g/l. The claims have been interpreted such that ribose esters are in the instant genus.

Please note that the term "prevent" is an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes).

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the art in preventing multiple organ dysfunction is unpredictable. Applicants own specification states that 'no effective treatments have been developed so far' (page 1 lines 22-23).

Seely et al. (Crit Care Med v28 2000 pages 2193-2200) teach that multiple organ dysfunction represents the most common cause of death in the intensive care unit (first paragraph page 2193). Seely teach that multiple organ dysfunction treatment is largely supportive (i.e. not preventative) (first paragraph page 2193). Seely teach that numerous clinical studies of therapy for patients with multiple organ dysfunction have been universally disappointing (first paragraph page 2193). Seely conclude (page 2198 section 'conclusions') that effective immunomodulation of a patient with multiple organ dysfunction represents the most difficult challenge facing critical care medicine.

Ciesla et al. (Arch Surg v140 May 2005 pages 432-440) teach that multiple organ failure remains a major source of morbidity and is the leading cause of in-hospital mortality despite more than 25 years of intense investigation (first sentence page 432).

Johnson et al. (Canadian Journal of Anesthesia v48 2001 pages 502-509) teach that therapy directed to prevent or improve multiple organ dysfunction has not dramatically altered outcomes (last line of 3rd paragraph 'results section' page 502).

Taken together, the state of the art in preventing multiple organ dysfunction is unpredictable.

(5) The relative skill of those in the art:

The level of skill in the art is high.

(2) The breadth of the claims

Although the claims are unclear (see 112 2nd) since the claims are drawn to administration prior to the occurrence of trauma the claims are interpreted as being open to

numerous causes of multiple organ dysfunction including trauma, pancreatitis, burns, shock, infection, aspiration, etc. (compare Steely et al. page 2193 last paragraph). Trauma includes such things as gunshot wounds and stabbings. It is noted that the claims are open to any and all degrees of severity of the trauma, for example multiple gunshot wounds.

As discussed above the term "prevent" is an absolute definition which means to stop from occurring. As such, the claims are drawn to prevention at any point in time in the future.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification provides examples of rat studies in which pre-operative supplementation was investigated (examples 8-9). The examples show the effects of supplementation (page 17-24) on various parameters such as intestinal permeability, bacterial translocation, and lung inflammation. The specification provides examples in which the effects of supplements for a cell line was investigated (page 25-26). It is noted that the composition used in example 8 (page 16) appears to include dextrin and fructose and the composition of example 9 (page 23) appears to include flavonoids. The instant claims require specific amounts of guanosine, a guanosine salt, GTP, or a guanosine ester. The examples do not appear to be commensurate in scope with the instant claims.

However, the specification does not provide examples of the treatment nor the prevention of any and all types of multiple organ dysfunction. In particular the examples are not drawn to mammals suffering from various types of trauma let alone cases including situations such as multiple gunshot wounds. Further, the specification does not provide guidance on how the

examples of intestinal permeability, bacterial translocation, and lung inflammation correlate to prevention of multiple organ dysfunction as a result of trauma.

One of skill in the art would not equate the effects of supplementation (page 17-24) with the ability to prevent multiple organ dysfunction. One would not extrapolate results from mammals that are not suffering from trauma to mammals that are suffering from trauma. Further, the specification does not provide any correlation between guanosine and carbohydrates and their ability to prevent multiple organ dysfunction. Although guanosine and carbohydrates may effect the metabolism of patients one would not equate altered metabolism with prevention of multiple organ dysfunction. Such guidance is necessary because the prior art cited above teach that the prevention of multiple organ dysfunction is unpredictable. As stated above, Seely et al. (Crit Care Med v28 2000 pages 2193-2200) teach that multiple organ dysfunction represents the most common cause of death in the intensive care unit (first paragraph page 2193). Seely teach that multiple organ dysfunction treatment is largely supportive (i.e. not preventative) (first paragraph page 2193). Seely teach that numerous clinical studies of therapy for patients with multiple organ dysfunction have been universally disappointing (first paragraph page 2193). Seely conclude (page 2198 section 'conclusions') that effective immunomodulation of a patient with multiple organ dysfunction represents the most difficult challenge facing critical care medicine.

Accordingly one would be burdened with undue experimentation to determine if the compositions of the current invention could be used in methods of prevention.

(8) The quantity of experimentation necessary:

Experimentation is required in numerous areas particularly related to how to use the method and determination if it would be useful for the prevention of multiple organ dysfunction.

Considering the state of the art as discussed by the references above, particularly with regards to the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Response to Arguments 112 1st

Since the claims have been amended, a new rejection adapted to the claims is recited above. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that the rationale of the rejection is similar to previous cases in which the rationale required precise predictability and 100% prevention. Applicants argue that the specification shows a beneficial effect and examples of mammal suffering from trauma.

Applicant's arguments filed 10/29/08 have been fully considered but they are not persuasive.

Although Applicants argue that the rationale of the rejection is similar to previous cases in which the rationale required precise predictability and 100% prevention, the rejection is based on numerous factors including the state of the prior art. As noted previously, Seely et al. (Crit Care Med v28 2000 pages 2193-2200) teach that multiple organ dysfunction represents the most common cause of death in the intensive care unit (first paragraph page 2193). Seely teach that multiple organ dysfunction treatment is largely supportive (i.e. not preventative) (first paragraph page 2193). Seely teach that numerous clinical studies of therapy for patients with multiple organ dysfunction have been universally disappointing (first paragraph page 2193). Seely conclude (page 2198 section 'conclusions') that effective immunomodulation of a patient with multiple

organ dysfunction represents the most difficult challenge facing critical care medicine. Ciesla et al. (Arch Surg v140 May 2005 pages 432-440) teach that multiple organ failure remains a major source of morbidity and is the leading cause of in-hospital mortality despite more than 25 years of intense investigation (first sentence page 432). Johnson et al. (Canadian Journal of Anesthesia v48 2001 pages 502-509) teach that therapy directed to prevent or improve multiple organ dysfunction has not dramatically altered outcomes (last line of 3rd paragraph 'results section' page 502). Applicants own specification states that 'no effective treatments have been developed so far' (page 1 lines 22-23). Taken together, the state of the art in preventing multiple organ dysfunction is unpredictable. As such, the state of the prior art differentiates the facts of the instant case from the facts of other cases.

Although Applicants argue that the specification shows a beneficial effect and examples of mammal suffering from trauma, the examples do not seem to be commensurate in scope with the instant claims. It is noted that the composition used in example 8 (page 16) appears to include dextrin and fructose and the composition of example 9 (page 23) appears to include flavonoids. The instant claims require specific amounts of guanosine, a guanosine salt, GTP, or a guanosine ester. The examples do not appear to be commensurate in scope with the instant claims. One of skill in the art would not equate the effects of supplementation (page 17-24) with the ability to prevent multiple organ dysfunction. One would not extrapolate results from mammals that are not suffering from trauma to mammals that are suffering from trauma. Further, the specification does not provide any correlation between guanosine and carbohydrates and their ability to prevent multiple organ dysfunction. Although guanosine and carbohydrates may effect the metabolism of patients one would not equate altered metabolism with prevention of multiple

organ dysfunction. Such guidance is necessary because the prior art cited above teach that the prevention of multiple organ dysfunction is unpredictable.

Claim Rejections - 35 USC § 102

Previously, claims were rejected under 102 using the reference cited below. Since the claims have been amended the rejection has been updated due to the amendments.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19,23-25,28-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Masor et al. (US 5,602,109).

Masor teach (claim 1) the administration of compositions comprising 60 to 110 g/l of carbohydrate and at least 70 mg/l of guanosine. Although Masor does not expressly recite the volumes administered, Masor teach typical intakes (ml/day) and feedings (#/day) (Table IX column 17). Further it is noted that there is no limitation in the instant claims as to whether or not the administration occurs in one feeding or multiple feedings. For example, the 831 ml/day as recited in column 17 line 32 corresponds to 50-91 g of carbohydrate and 58 mg guanosine. Thus Masor meet the ranges recited in the instant claims. Masor teach that glucose is a specific example of a carbohydrate of the invention (column 5 line 40). Masor teach the composition as a liquid (claim 2 for example) and teach enteral administration (column 5 line 40) thus meeting the limitations of claims 28-29 of the instant invention.

It is noted that the current claim is drawn to a method of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administrations. Masor teach the active method steps thus meeting the claim limitations. It is noted that there are no specific steps of surgery in the instant claims.

Although the claims are unclear (see 112 2nd) the claims are given the broadest reasonable interpretation (see MPEP section 2111). Since the claims are drawn to administration prior to the occurrence of trauma (see claim 25) the claims are interpreted as being open to administration prior to any type of trauma. The guanosine equivalents recited in claim 29 have been interpreted as referring to guanosine, otherwise the claim would not further limit the previous claim. The claims have been interpreted such that there is at least one soluble carbohydrate of at least 10 g/l. The claims have been interpreted such that ribose esters are in the instant genus.

Response to Arguments 102 - Masor

Since the claims have been amended, a new rejection adapted to the claims is recited above. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that Masor is directed to enhancing the immune system and is not disclosed to prevent multiple organ dysfunction. Applicants argue that claim 19 recites the method is for a mammal suffering from trauma.

Applicant's arguments filed 10/29/08 have been fully considered but they are not persuasive.

Although Applicants argue that Masor is directed to enhancing the immune system and is not disclosed to prevent multiple organ dysfunction, it is noted that the active step of the instant claims is administering a particular composition. The intended use for the administration does not take away from the fact that the composition was administered.

Although Applicants argue that claim 19 recites the method is for a mammal suffering from trauma (page 15), it is noted that applicants state (page 11 of reply) that claim 19 is drawn to patients who have or will suffer from trauma. Those who will suffer from trauma do not necessarily have trauma. As such the applicants contradictory arguments that the patient is one who suffers from trauma yet is one who is not yet suffering from trauma is evidence that the metes and bounds of the claims are unclear. As such, in accord with section 2111 of the MPEP the claims are given the broadest reasonable interpretation.

Conclusion

The prior art that remains of record and not relied upon is considered pertinent to applicant's disclosure. EP 0302807 as cited in the IDS specifically example VII table X page 20 remains of record.

Previously, claims were rejected under 112 2nd. Since the claims have been amended the rejection has been updated due to the amendments. Previously, claims were rejected under 112 1st - enablement. Since the claims have been amended the rejection has been updated due to the amendments. Previously, claims were rejected under 102 using the reference cited above. Since the claims have been amended the rejection has been updated due to the amendments.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action. Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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